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Rifadin (Rifampicin) in the treatment of gonorrhoea in Uganda

A controlled trial

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A number of recent surveys have shown an alarmingly high incidence of diminished penicillin sensitivity among strains of *Neisseria gonorrhoeae* isolated in Uganda (Phillips, Fernandes, Pirani, and Wagaine, 1969; Arya and Phillips, 1970; Arya, Pearson, Rao, and Blowers, 1970). About 80 per cent. of gonococcal strains from the Kampala area show diminished sensitivity to penicillin at the present time, and such strains also exhibit slightly diminished sensitivity to tetracycline and total resistance to streptomycin (Phillips and others, 1969; Arya and Phillips, 1970). Phillips and others (1969) also observed links in the sensitivity pattern between penicillin and other unrelated antibiotics—notably erythromycin, chloramphenicol, and gentamycin. Similar links have also been described elsewhere (Reyn and Bentzon, 1968, 1969; Phillips, Rimmer, Ridley, Lynn, and Warren, 1970). If conditions and practices responsible for the decline in usefulness of penicillin and other drugs are allowed to continue, then we may be 'witnessing the emergence of a multiple-resistant gonococcus' (Phillips and others, 1969) at least in this part of the world with a very high incidence of gonorrhoea. Moreover we are already reaching the limit of the amount of procaine penicillin (2·4 mega units) that can reasonably be given in one injection.

For these reasons it is important to search for alternative drugs. Rifadin (rifampicin), a semi-synthetic oral antibiotic, has already been reported to give satisfactory results (Willcox, Morrison, and Cobbold, 1970), and no toxic effects were reported with the dosage used. It was therefore decided to evaluate this drug in a population with a high incidence of gonorrhoea and very amenable to follow up (Arya and Phillips, 1970).

Material and methods

PATIENTS

254 male university students suffered 357 attacks of urethritis (gonococcal and nongonococcal) between August, 1969, and July, 1970. 66 patients had their first-ever attack of urethritis during this study; the rest (*i.e.* 188 patients) had already had one to eight attacks of urethritis during their stay in the university. 327 attacks of urethritis seen and treated by one of us (O.P.A.) formed the basis of this study.

LABORATORY INVESTIGATIONS

Gram-stained urethral smears were made in all cases, and cultures in 279 cases. Gonorrhoea was diagnosed if characteristic Gram-negative bean-shaped intracellular diplococci were seen and/or if gonococci were grown on culture. Nongonococcal urethritis was diagnosed if such organisms were neither seen nor grown.

Disc-diffusion sensitivity tests to Rifadin were performed on chocolate agar cultures; the discs were supplied by Lepetit Pharmaceuticals, Nairobi (Kenya branch). Minimum inhibitory concentrations of penicillin were determined as described by Arya and Phillips (1970), with the exception that the Oxford staphylococcus was used instead of W.H.O. reference strains.

Blood samples were taken for routine serum tests for syphilis.

TREATMENT

Six capsules of Rifadin (rifampicin), each containing 150 mg. of the antibiotic, were swallowed with water by the patient in the presence of the physician. Each patient so treated was warned of the transient reddish discoloration of the urine which would be produced by the drug. Procaine penicillin (Flopen-Hoechst) 2·4 mega units intramuscularly in one dose was used in control cases—this being the routine treatment of gonorrhoea in the student clinic. The patients were randomly allocated to one of these treatment schedules. A few patients were also treated with eight capsules of Rifadin (1,200 mg.) given in a single dose.

FOLLOW-UP

Return visits were arranged 3 days, 1 week, 2 weeks, 3 weeks, and 3 months after treatment. Most patients were seen early in the morning, having held their urine all night, and the rest were seen later in the day after urine had been held for at least 3 hours. At each visit, after questioning about re-exposure and after clinical examination, any discharge was sampled and examined bacteriologically; two-glass urine tests were performed and the urine was examined for haze and threads; a Gram-stained smear was made of the threads if present. Prostatic massage was done only if symptoms or signs warranted it. If a patient failed to attend within 2 weeks, a letter was sent

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to him or he was visited in his room and later seen in the clinic as well. If all was well after 3 weeks, the patient was asked to return at the end of 3 months for final tests, but to come earlier if necessary. Some who attended earlier for other complaints were checked for venereal disease as well.

Patients in whom infection failed to respond to one treatment schedule were treated with the other schedule, or with Rifadin 1,200 mg. (*i.e.* eight capsules), or some other drug known to be effective.

Results

Of 327 episodes of urethritis seen in this study, 203 were diagnosed as cases of gonorrhoea. Of these 164 were seen within 2 days after the appearance of discharge, 37 within 3 to 6 days, and two after 7 days. Sources of infection were casual acquaintances or prostitutes in 104 cases, continuing acquaintance or friend in 84, wife in five, and a male friend in one case; in the remaining nine cases the source of infection could not be determined because multiple contacts had taken place within the space of a few days. Ten patients had previously been treated elsewhere (including self-treatment in two cases). Of the 169 patients who contracted these 203 attacks of gonorrhoea, fourteen were married.

FOLLOW-UP

Data on follow-up are given in Table I. About 60 per cent. of cases were followed up for more than 4 weeks. Most of the shorter periods of follow-up were seen in students who were re-infected. Almost one-third of re-infections had taken place within 4 weeks. The thirteen patients followed for less than 2 weeks include ten who were considered to be re-infected after having admitted to re-exposure; the remaining three were lost to the study, having left the university soon after treatment.

TABLE I *Follow-up*

Follow-up period (wks)	12	9–11	5–8	3–4	2	*less than 2*	*Total*
Number of cases	52	23	44	50	21	13 (3 defaulters)	203 (200)

BACTERIOLOGICAL RESULTS

From the 203 cases diagnosed as gonorrhoea during the clinical trial, 146 cultures were made, of which 125 were positive (only three of these had negative smears); 84 unselected cultures of the gonococcus were tested for penicillin sensitivity, and 69 (82 per cent.) showed diminished sensitivity (Table II)—a figure which is very similar to those reported earlier (Arya and Phillips, 1970; Arya and others, 1970). 112 strains were tested for sensitivity to Rifadin by the disc-diffusion method; all except one were sensitive, and this one was later reported to be sensitive after having been flown to Italy for further tests (Gruppo Lepetit, personal communication). The infection caused by this strain did not respond to the Rifadin schedule of 900 mg.

TABLE II *Penicillin sensitivity of gonococci*

	Sensitive		*Less sensitive*		
Penicillin minimum inhibitory concentration (μg./ml.)	0·03	0·06	0·12	0·24	0·48
Number of strains	5	10	15	27	27
Percentage	18		82		

RESULTS OF TREATMENT

Of the 203 cases, 102 received procaine penicillin 2·4 m.u. and 90 were treated with Rifadin 900 mg. (both randomly allotted) (Table III). The remaining eleven received Rifadin 1,200 mg. (Table IV, overleaf).

Schedule 1 (Procaine penicillin 2·4 m.u.) gave a cure rate of 89·5 per cent.

Schedule 2 (Rifadin 900 mg. in a single dose) gave a cure rate of 87·1 per cent. One patient complained of anorexia, nausea, and salivation 10 days after the administration of Rifadin. On examination he looked well; the temperature was normal; the liver was just palpable, firm and not tender; the white blood cell count was normal; the serum bilirubin and transaminases were normal. His symptoms disappeared after a few days, and he remained well during a follow-up period of 6 months.

TABLE III *Treatment results*

Schedule	*No. of episodes*		*Results*			
	Treated	*Followed*	*Failed*	*Concomitant NGU*	*Re-infected*	*Cured per cent.*
(1) Procaine penicillin (2·4 m.u.) intramuscularly (one dose)	102	100	10	27	5	89·5
(2) Rifadin 900 mg. orally (one dose)	90	89	11	14	4	87·1

Table III includes the records of six patients who had been treated unsuccessfully before coming to our clinic; all these had reputedly received penicillin in varying amounts and some had also received a few capsules. Three such patients received 2·4 m.u. procaine penicillin and only one was cured; the other three received 900 mg. Rifadin and all were cured.

Five of the 21 cases of failure from the above two schedules were treated with Rifadin 1,200 mg. in a single dose, and four were cured. Eleven further cases, as already mentioned, were also treated with Rifadin 1,200 mg. in a single dose and ten were cured. The results in these sixteen cases are shown in Table IV. Four of the sixteen already treated unsuccessfully elsewhere were cured with Rifadin 1,200 mg. Thus Rifadin 1,200 mg. gave a cure rate of 86·7 per cent. in a small number of cases which had failed to respond to previous treatment.

Three of the remaining cases of failure were treated and cured with a combination of procaine penicillin 2·4 m.u. in one injection, and 1g. Ampicillin (Penbritin, Beecham Research Laboratories) given orally at the same time.

Discussion

Our criteria for defining failure and distinguishing relapse from reinfection were same as have been described earlier (Arya and Phillips, 1970; Arya and others, 1970). Of the 23 cases of failure seen in this study, twenty were seen in the first week and the remaining three in the second week. Similar observations were made in the studies just quoted. Ten cases considered to be due to re-infection within 2 weeks on the basis of history of re-exposure were classed neither as failures nor as cures.

Although the makers have recommended that Rifadin should be administered on an empty stomach to ensure rapid and complete absorption (Lepetit, 1968) it was not always possible to do this. The drug was administered as soon as the diagnosis of gonorrhoea was made. As Table V indicates, the time elapsed since the last meal did not have any consistent effect on the results of treatment. Willcox and others (1970) also found no significant relationship between the time of the last meal and the effect of the dose.

Our results show that one dose of Rifadin 900 mg. gives cure rates conparable with 2·4 m.u. of procaine penicillin. Although the number of cases treated with eight capsules (1,200 mg.) Rifadin in this study is small, the results indicate that increasing the dose from 900 mg. to 1200 mg. may not improve its performance.

TABLE V *Relationship of Rifadin treatment results to the time of last meal*

Hours since last meal	*No. treated*	*No. followed**	*Failed*	
			No.	*Per cent.*
1–2	28	26	4	15·4
3–4	54	52	7	13·5
5–8	11	11	—	—
Empty stomach (overnight)	13	11	2	18·2
Total	106	100	13	13·0

*Five cases re-infected, have been excluded from these figures

Rifadin apparently has several good features—it is safe in the dosage used and it can be administered in one dose under the doctor's supervision, unlike several other effective oral treatment schedules (*e.g.* tetracyclines and trimethoprim-sulphamethoxazole) which have to be taken in multiple doses. It does not seem to mask concurrent syphilitic infection, for two patients treated with Rifadin in this study later developed syphilitic penile chancres and enlargement of the regional lymph glands.

One of these patients developed a sore one week after Rifadin treatment, had intercourse again (while the sore was present) and acquired another attack of gonorrhoea for which he again received Rifadin 900 mg. Although advised to report for darkfield examination, he did not return until 10 days later when the sore had increased in size; a darkfield examination done at this time showed a large number of *Treponema pallidum* organisms. His serum tests for syphilis which were negative when the sore was first seen had become positive at the subsequent visit 10 days later.

The second patient presented himself 8 weeks after treatment with Rifadin with a typical syphilitic penile chancre of at least 2 weeks' duration and enlargement of regional lymph glands. He denied any further sexual exposure. Darkground examination showed *Treponema pallidum* and serum tests for syphilis were also positive, having been negative when he first reported.

More elaborate observations in this connection have been made by Fuga and Gentili (1968).

However, in view of its potential in the treatment of tuberculosis, it is suggested that Rifadin should not be used routinely for the treatment of gonorrhoea

TABLE IV *Treatment results with Rifadin 1,200 mg.*

No. treated	*No. followed*	*Failed*	*Concomitant NGU*	*Re-infected*	*Cured, per cent.*
16	16	2	5	1	86·7

lest such wide use should undermine its value in tuberculosis for which few safe alternatives are available. In our view its use in gonorrhoea should be restricted to the treatment of resistant cases and possibly for those in whom penicillin is contra-indicated.

Summary

A trial of Rifadin (rifampicin) compared with penicillin in the treatment of 203 cases of gonorrhoea is described. Six capsules each of 150 mg. given in a single dose yielded a cure rate of 87·1 per cent., compared to the 89·5 per cent. achieved by procaine penicillin 2·4 m.u.

Rifadin appeared to be free from toxic effects in the dosage used. There was evidence that it did not mask concurrent syphilitic infection. In view of its potential in the treatment of tuberculosis, the authors advise that this drug should be used in gonorrhoea only as an alternative in special circumstances.

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Addendum

Since this paper was submitted our attention has been drawn to certain recent publications, notably that of Nitti (1969), which suggest that rifampicin resistance among strains of tubercle bacilli may not appear until after about one month's treatment with this drug.

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Rifadin (rifampicin) dans le traitement de la gonococcie en Ouganda. Un essai controlé

SOMMAIRE

On rapporte un essai de la Rifadin (rifampicin) dans le traitement de 203 cas de gonococcie. Six capsules de 150 mg. chacune furent données en une seule prise avec un taux de guérison de 87,1 pour cent, contre 89,5 pour cent avec 2,4 méga-unités de pénicilline-procaïne. La Rifadin apparaît exempte d'effets toxiques à la posologie utilisée. Il fut prouvé qu'elle ne masque pas une infection syphilitique concomittante. En pensant aux possibilités de traitement de la tuberculose, les auteurs attirent l'attention sur le fait que le médicament ne doit être utilisé dans la gonococcie que dans des circonstances spéciales de remplacement.